renders claims 1, 3-8, and 10-14 obvious. Submitted herewith is the terminal disclaimer and accompanying fee.

Claim Rejections and 35 U.S.C. § 103(a)

Claims 1, 3-8, and 10-14 stand rejected under 35 U.S.C. § 103(a) as allegedly being anticipated by U.S. Patent Application 20040013661 as evidenced by Merck Index (17th ed. 1999, p.1145, 1146, 1841-1848, 2539, & 2550), Dwinnell *et al.* (Atlas of Diseases of the Kidney, Ch. 12, 1999) ("Dwinnell"), Merriam Webster's Dictionary (p. 82 1999), and U.S. Patent 5,273,961 ("Clark"). Applicants respectfully traverse the rejection.

A framework for applying the statutory language of §103 is set out in *Graham v. John Deere Co. of Kansas City*, 383 U. S. 1 (1966):

> "Under §103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented."

Id., at 17–18.

To establish a *prima facie* case of obviousness, the prior art itself or "the inferences and creative steps that a person of ordinary skill in the art would [have] employ[ed]" at the time of the invention are to have taught or suggested the claim elements. Additionally, there must have been "a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements" in the manner claimed. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1742, 167 L.Ed.2d 705, 75 USLW 4289, 82 USPQ2d 1385 (2007). "Often, it will be necessary for a [fact finder] to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed...To facilitate review, this analysis should be made explicit." *Id.* "[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be

some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006). Furthermore, to establish a *prima facie* case of obviousness there must have been a reasonable expectation of success. M.P.E.P. § 2143.02. Underlying the obvious determination is the fact that statutorily prohibited hindsight cannot be used. *KSR*, 127 82 USPQ2d at 1385.

"A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning. *See Graham*, 383 U.S. at 36 (warning against a 'temptation to read into the prior art the teachings of the invention in issue' and instructing courts to 'guard against slipping into the use of hindsight'" (quoting *Monroe Auto Equipment Co. v. Heckethorn Mfg. & Supply Co.*, 332 F. 2d 406, 412 (CA6 1964)))." *Id.* at 1397.

Independent claim 1 recites "[a] method of treating acute renal failure in a subject, the method comprising: administering to the subject a composition comprising an oligopeptide having activity in treating acute renal failure, said oligopeptide comprising the sequence QGV or MTRV (SEQ ID NO:1), wherein said oligopeptide is from three (3) to twelve (12) amino acids in length."

Applicants submit that a *prima facie* case of obviousness has not been established. Regarding claim 1, applicants respectfully submit that the Office failed to show a correlation between NO production and BUN. The Office asserts that "the AQGV peptide is known to reduce production of NO, reducing BUN ([0047]), in particular." *Office Action* mailed January 15, 2008, page 3. While Wensvoort describes use of a composition that "comprises at least two oligopeptides...each capable of down regulating NFkB, and thereby reducing production of NO," Wensvoort does not mention BUN at all. *Wensvoort*, at paragraph [0047]. The references cited by the Office do not establish a relationship between NO production and BUN. The Office seems to suggest that it would have been obvious to combine the administration of AQGV as described in Wensvoort (AQGV lowering NO production) with Dwinnel *et al.* (knowledge that acute renal failure patients have high BUN) and Clark (treatment of acute renal failure by decreasing BUN). However, no evidence has been presented that reducing NO production in a cell will result in reduced BUN in a subject. On the contrary, applicants point out that research

in the field of nephrology indicates that an increase in urea concentration may be responsible for an inhibitory effect on NO production which further leads to medical complications associated with uremia. (*Prabhakar et al.* Am. J. Physiol 273:1882-1888, 1997 and *Xiao et al.*, Am. J. Physiol. Renal Physiol. 280:989-995, 2001; both references have been submitted with the IDS filed herewith). Therefore, research indicates that high urea levels may lead to low NO production and not, as the Office suggests, that decreased NO production necessarily leads to a decrease in BUN. Any knowledge correlating the AQGV peptide with either a method of treating acute renal failure or reducing BUN is gleaned only from the applicants' Specification and is a hindsight attempt to gather elements for bringing them together with the benefit of applicants' disclosure.

Additionally, applicants respectfully disagree that the Clark reference "teaches that the treatment of acute renal failure can be achieved by decreases of blood urea nitrogen (col. 12, under Example[s])." *Office Action* mailed January 15, 2008, page 3. Clark discloses a method of treating a mammal at risk of acute renal failure ("ARF") by administering an effective amount of IGF-I. *Clark*, Abstract. IGF-I is thought to affect the cellular composition of renal cortical slices and to restore normal renal function in ARF by normalizing the effectiveness of the cationic transporters in the renal cortical slices. *Id.*, at paragraph 27, lines 15-20 and 42-29. Des-IGF-I is thought to exhibit anabolic growth promoting effects during ARF by accelerating the recovery of renal function via its growth factor. *Id.*, at paragraph 30, lines 7-10. Clark states that clinical symptoms of kidney damage include increased blood urea nitrogen or creatinine levels. *Id.*, at paragraph 8, lines 43-47. Clark only measures BUN levels in order to assess the response of the animal to the IGF-I treatment since BUN and creatinine "are accepted indicators of renal function." *Id.*, at paragraph 12, lines 18-29. Clark never treats BUN directly, but instead administers the IGF-1 treatment and measures success by measuring the BUN and creatinine levels of the animal, both of which are indicative of general renal function. Any decrease in BUN in response to the administration of IGF-1 is merely the method the researchers chose to evaluate renal function. The IGF-1 treatment results in affecting the cellular composition of the renal cortical slices in such a way as to return to normal the effectiveness of the cationic transporters. *Id.*, paragraphs 27, 43-47. Therefore, the Office has failed to show that treatment

with the peptides recited in claim 1 would have been predictable to a person of ordinary skill in the art. Accordingly, applicants respectfully request withdrawal of this 35 U.S.C. § 103(a) rejection.

Claim 5 is further allowable because the definition of "bolus" as used by the Office is inconsistent with the usage in Wensvoort or in the art. The Office alleges that Wensvoort teaches oral administration of the AQGV peptide because Wensvoort states that the peptide "can also be given in a bolus injection." Wensvoort, paragraph [0045] (emphasis added). The Office reasons that since a bolus is defined as "a rounded mass, soft mass of chewed food" it must include oral administration. *Office Action* mailed January 15, 2008, page 3. However, the Office ignores the term injection as used in Wensvoort which is much more consistent with the alternative definition of an injectable bolus ("a large dose of a substance given by injection for the purpose of rapidly achieving the needed therapeutic concentration in the bloodstream") as seen in the online Merriam-Webster Medical Dictionary (available at http://medical.merriam-webster.com/medical/bolus). Therefore, Wensvoort and the other cited references do not cover oral administration of the peptides of claim 5. Accordingly, applicants respectfully request withdrawal of this 35 U.S.C. § 103(a) rejection.

As provided for by the Office's own guidelines, in order to make an obviousness rejection such as that set forth in the final Office action, the Office "must resolve the *Graham* factual inquiries". *See, e.g., M.P.E.P.*, § 2143 A(1) ("Examples of Basic Requirements of a *Prima Facie* Case of Obviousness"). Contrary to the Office's own guidelines, however, the instant obviousness rejections never resolve what the level of ordinary skill in the pertinent art was at the time of the invention, which is required. *See, M.P.E.P.*, § 2141 II.

Moreover, in making its rejections, the Office did not explicitly articulate under what rationale the legal conclusion of obviousness is supported as required by KSR. *See, e.g., M.P.E.P.*, § 2142. Applicants are left to guess what rationale the Office may have used from the list of exemplary rationales cited under *M.P.E.P.*, § 2143. Assuming that the Office has chosen Rationale A ("Combining Prior Art Elements According to Known Methods To Yield Predictable Results") the Office fails to articulate a finding that one of ordinary skill in the art could have combined the elements as claimed by known methods, and that, in combination, each

element merely performed the same function as it does separately. *See, e.g., M.P.E.P.*, § 2143 A(2). In fact, the Office cannot do so in the instant case because elements of applicants' claims do not merely perform the same function as they allegedly separately did in the cited references. The Office's guidelines, however, specifically require the Office to make such a finding. *Id.*

In making its obviousness rejections, the Office has also not articulated a finding that one of ordinary skill in the art would have recognized that the results of the proposed combination were predictable. *See, e.g., M.P.E.P.*, § 2143 A(3). Again, however, the Office's guidelines specifically require such a finding.

Applicants further point out that the Office has the initial burden of showing a *prima facie* case of obviousness in a 35 USC 103(a) rejection. *M.P.E.P.* § 2142. The Office states that "the invention as a whole is prima facie obviousness...as evidenced by the references, especially in the absence of evidence to the contrary." *Office Action* mailed January 15, 2008. page 4. Applicants are not obligated to rebut a claim of obviousness with evidence until a *prima facie* case of obviousness has been shown by the examiner. *Id.* However, a *prima facie* case of obviousness has not been shown here. Moreover, the cited language seems to suggest that the Office considered the "lack of evidence to the contrary" in its decision to reject the claims under 35 USC 103(a). This action improperly shifts the burden from the Office to the applicants and is impermissible.

Furthermore, claim 1 is nonobvious because no reason exists that would have prompted a person of ordinary skill in the relevant field to combine the prior art elements in the manner claimed. The Office alleges that Wensvoort teaches administration of AQGV peptide which "is known to reduce production of NO, reducing BUN." *Office Action*, mailed January 15, 2008, page 3. As applicants previously discussed however, Wensvoort does not teach or suggest any correlation between NO production and BUN in a subject. Additionally, the Office admits that Wensvoort does not teach or suggest the method of treating acute renal failure with the administration of a pharmaceutical composition comprising AQGV peptide. *Id.* The Office cites Dwinnel *et al.* to show that patients with acute renal failure have high BUN concentrations. Additionally, the Office cites Clark to illustrate that acute renal failure can be treated by lowering BUN. However, as previously shown, Clark merely teaches what Dwinnel *et al.* teaches, *e.g.*,

that patients with acute renal failure have high BUN concentrations. Clark only measures BUN levels in animals in order to assess renal condition. A person of ordinary skill in the art having common sense would not predictably combine the references as suggested by the Office. The Office has not shown a nexus between the problem of treating acute renal failure and the problem of treating ischemia reperfusion injury. The lack of such nexus shows that the combination of the alleged prior art elements does not lead an artisan having common sense to a predictable result. The Office uses statutorily prohibited hindsight in combining the alleged prior art elements to arrive at claim 1 because nothing in the prior art exists linking the administration of AQGV peptides with the treatment of acute renal failure or the lowering of BUN concentrations in a subject. Accordingly, applicants respectfully request the withdrawal of the 35 U.S.C. § 103(a) obviousness rejection of claim 1.

Additionally, claims 3-8 and 10-14 are nonobvious for at least the same reason as is claim 1. Applicants respectfully request the withdrawal of the 35 U.S.C. § 103(a) obviousness rejection of claims 1, 3-8 and 10-14.

Applicants believe the application is in condition for allowance, and a notice of allowance is kindly solicited. If, however, questions remain after consideration of the foregoing, the Office is kindly requested to contact applicants' attorney at the address or telephone number given herein.

Respectfully submitted,

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